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EXAMINER	
THOMAS, DAVID C	
ART UNIT	PAPER NUMBER
1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,441	BURGGRAF, SIEGFRIED	
	Examiner	Art Unit	
	David C. Thomas	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-47* is/are pending in the application.

4a) Of the above claim(s) *45-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/28/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of Group 1, claims 25-44 in the reply filed on December 15, 2006 is acknowledged. Claims 45-47 are withdrawn from further prosecution. The traversal is on the grounds that the Wittmer reference does not anticipate or render obvious the methods claims. This is not found persuasive for several reasons. Applicant argues that Wittmer does not teach a single-stranded control nucleic acid and therefore does not anticipate one or more of the methods claims. Since the genomic DNA that is provided as the control DNA is denatured during the initial PCR step, single-stranded nucleic acid is provided in the sample prior to amplification. In addition, Wittmer teaches the testing of viral load in patients infected with HIV and hepatitis C for purposes of prognosis and therapy (column 11, lines 54-60). Furthermore, genomic DNA is known to inherently contain single-stranded regions and therefore single-stranded control nucleic acid is provided in the assay. Finally, Wittmer also teaches the use of detection probes capable of differentiating between the target and control products due to differing melting temperatures. Therefore, Wittmer anticipates at least one or more of the methods claims.

The requirement is still deemed proper and is therefore made FINAL.

Claim Objections

2. Claim 41 is objected to because of the following informalities: Claim 41 is dependent upon itself. Appropriate correction is required.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 25-39 and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by Wittwer et al. (U.S. Patent No. 6,174,670).

Wittwer teaches a method for qualitative or quantitative detection of a nucleic acid in a sample (for overview, see Abstract and column 4, lines 32-50), said method comprising the steps of:

amplifying a nucleic acid to be detected in a sample in the presence of at least one single-stranded detection probe that by a reversible binding action binds reversibly to a binding region of said nucleic acid to be detected and enables a detection of said nucleic acid to be detected based on said reversible binding action (target DNA is amplified using pair of primers in presence of two probes which hybridize to adjacent regions of target during annealing phase of PCR at each cycle, column 3, 58-61, column 7, lines 56-67 and Figure 18, top example; see Figure 2 for probe annealing during phase of lowered temperature);

providing a single-stranded control nucleic acid in said sample and amplifying said single-stranded control nucleic acid in said sample, wherein said single-stranded control nucleic acid has a binding region that also binds said at least one single-stranded detection probe and wherein said binding region of said single stranded

control nucleic acid has a nucleotide sequence having at least one deviation in comparison to said nucleotide sequence of said binding region of said nucleic acid to be detected (two nucleic acid targets having difference at selected locus are present in reaction which have binding sites for two probes which hybridize at adjacent sites in target wherein one of the probes spans the locus site and is matched with one of the targets and therefore deviates from the sequence of control target, column 7, lines 53-54 and line 64 to column 8, line 9; see Figure 18 for dual probe annealing; genomic DNA that is provided as the control DNA is denatured during the initial amplification step, and therefore is in single-stranded form, while the nucleic acid of some pathogens such as HIV used for the testing of viral load in patients infected with HIV for purposes of prognosis and therapy is inherently single-stranded (column 11, lines 54-60).

wherein a first product of said nucleic acid to be detected and of said at least one single-stranded detection probe and a second product of said single-stranded control nucleic acid and of said at least one single-stranded detection probe have different melting points and a temperature difference of said melting points is sufficiently large to analytically differentiate said first and second products from one another for carrying out said detection (temperature melting profiles for each target sample are generated that are distinguishable if a true sequence deviation exists between the targets, column 7, line 64 to column 8, line 9 and column 8, lines 25-35; see also Example 23, column 46, lines 20-48, for detection of heterozygous and homozygous forms of methylenetetrahydrafolate reductase (MTHFR) gene and Figure 48).

With regard to claim 26 and 27, Wittwer teaches a method for qualitative or quantitative detection of a nucleic acid in a sample wherein said melting point of said second product is lower than said melting point of said first product by at least 5°C. (for analysis of point mutation in MTHFR gene, melting point of homozygous mutant is lower than that of wild-type by about 5°C, column 46, lines 20-48 and Figure 48).

With regard to claim 28, Wittwer teaches a method for qualitative or quantitative detection of a nucleic acid in a sample wherein said single-stranded control nucleic acid and said nucleic acid to be detected are amplified with identical primers (amplification of both control and target nucleic acids are performed with same primers, column 46, lines 27-34).

With regard to claim 29, Wittwer teaches a method for qualitative or quantitative detection of a nucleic acid in a sample wherein said nucleic acid to be detected and said single-stranded control nucleic acid are amplified by polymerase chain reaction (amplification of control and target nucleic acids is achieved by PCR, column 8, lines 10-18 and column 46, lines 34-46).

With regard to claim 30, Wittwer teaches a method for qualitative or quantitative detection of a nucleic acid in a sample wherein two or more of said nucleic acid to be detected and two or more of said single-stranded control nucleic acid are present in said same sample and wherein for each one of said nucleic acids to be detected one of said single-stranded control nucleic acids is present (the discriminatory power of hybridization probes can be applied to multiplex PCR using multiple detection probes

that sequentially melt off different targets at different temperatures, column 46, lines 49-61).

With regard to claim 31, Wittwer teaches a method for qualitative or quantitative detection of a nucleic acid in a sample wherein said nucleic acid to be detected is a DNA or an RNA derived in particular from a pathogen (nucleic acid from pathogens such as hepatitis B and C, and HIV can be detected using hybridization probes that distinguish wild-type and variants by melting curve profiles, column 35, lines 30-60 and column 41, lines 54-60).

With regard to claim 32, Wittwer teaches a method for qualitative or quantitative detection of a nucleic acid in a sample wherein said detection of said nucleic acid to be detected is carried out in real-time (monitoring of factor V Leiden mutation can be monitored both in real time during each cycle, as well as by performing melting profile after completion of amplification, column 44, line to column 45, line 14 and Figures 46 and 47).

With regard to claim 33, Wittwer teaches a method for qualitative or quantitative detection of a nucleic acid in a sample wherein said detection is carried out at a temperature that is 2°C to 10°C below said melting temperature of said first product (monitoring of fluorescence begins at 50°C during melting profile measurements, more than 2°C but less than 10°C below melting temperature of homozygous mutant control for MTHFR gene example, column 46, lines 42-46 and Figure 48).

With regard to claim 34, Wittwer teaches a method for qualitative or quantitative detection of a nucleic acid in a sample wherein said melting point of said second

product is so low that said second product is negligible or not at all present in said detection (melting point of homozygous mutant is comparatively low for factor V Leiden mutation and product appears not be present when monitoring sample at 63°C where both heterozygous and homozygous wild-type are not fully melted, column 44, line 65 to column 45, line 14 and Figure 47).

With regard to claim 35, Wittwer teaches a method for qualitative or quantitative detection of a nucleic acid in a sample wherein only one of said at least one single-stranded detection probe is used and said detection of said nucleic acid to be detected is based on a melting curve of said nucleic acid to be detected in the presence of said at least one single-stranded detection probe, wherein a melting curve of said single-stranded control nucleic acid in the presence of said at least one single-stranded detection probe serves as an internal control of proper amplification (example of melting profile for monitoring MTHFR gene mutation is performed using one labeled probe along with a labeled primer, wherein control nucleic acid is amplified and monitored by performing melting curve, which is indicative of proper amplification, column 46, lines 20-48 and Figure 48).

With regard to claim 36, Wittwer teaches a method for qualitative or quantitative detection of a nucleic acid in a sample wherein two of said at least one single-stranded detection probe are used, wherein a first one of said two single-stranded detection probes carries a reporter group and a second one of said two single-stranded detection probes changes observable properties of said reporter group when in a position in the vicinity of said reporter group (two labeled hybridization probes can be used wherein the

probes hybridize at closely spaced sites on the target, with one probe being 3'-labeled with fluorscein to allow transfer of energy to nearby Cy5 reporter group on 5' end of second probe, column 31, line 43 to column 32, line 7 and Figure 18).

With regard to claim 37, Wittwer teaches a method for qualitative or quantitative detection of a nucleic acid in a sample wherein said at least one single-stranded detection probe carries a reporter group and a second group that changes observable properties of said reporter group when in a position in the vicinity of said reporter group, wherein said reporter group and said second group are positioned so close to one another that said observable properties of said reporter group are changed either only during binding of said at least one single-stranded detection probe to said nucleic acid to be detected or only in a non-bonded state of said at least one single-stranded detection probe (dual-labeled probes can be used wherein the reporter and second group are subject to quenching of the fluorescence signal when not hybridized, wherein observable properties are changed upon binding to a target during amplification whereupon the probe is cleaved to further increase the signal, column 21, lines 47-49, column 28, lines 48-55, and Figure 5B).

With regard to claim 38, Wittwer teaches a method for qualitative or quantitative detection of a nucleic acid in a sample wherein said nucleotide sequence of said single-stranded control nucleic acid in said binding region for said at least one single-stranded detection probe has at least one modification relative to said nucleic acid to be detected (single base mutations are detected in samples containing factor V Leiden mutation (column 42, lines 62-64) as well as MTHFR gene mutation, column 46, lines 20-26).

With regard to claim 39, Wittwer teaches a method for qualitative or quantitative detection of a nucleic acid in a sample wherein said at least one modification is an exchange of a G or a C (factor V Leiden mutation involves G to A mutation, column 42, lines 62-64, while MTHFR gene mutations involves C to T mutation, column 46, lines 20-26).

With regard to claim 42, Wittwer teaches a method for qualitative or quantitative detection of a nucleic acid in a sample wherein a sequence region of said single-stranded control nucleic acid that can neither hybridize with said at least one single-stranded detection probe nor optionally with a primer is shortened (probes can be designed to detect deletion mutations, such that shortened version of control nucleic acid will have lower melting temperature and thus not hybridize at certain temperatures during melting profile, column 45, lines 60-67).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 40, 41, 43, and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wittwer et al. (U.S. Patent No. 6,174,670) in view of Picard et al. (U.S. Patent No. 6,265,170).

Wittwer teaches the limitations of claims 25-39 and 42 as discussed above.

Wittmer does not teach a method for qualitative or quantitative detection of a nucleic acid in a sample wherein said nucleotide sequence of said single-stranded control nucleic acid in said binding region for said at least one single-stranded detection probe has at least three modifications relative to said nucleic acid to be detected. Wittmer also does not teach a method wherein the probe fails to hybridize with a probe or primer because of modifications relative to the nucleic acid to be detected, and wherein the modifications are distributed approximately uniformly across said binding region for said at least one single-stranded detection probe.

Picard teaches a method for measuring binding affinity of nucleic acid probes for reference and target molecules by application of voltage to test samples, including probes that contain mismatches or deletions relative to the target such as one- to three-base mismatches and one- to three-base deletions (column 2, line 51 to column 3, line 6) and probes containing 3 noncontiguous mismatches distributed evenly over the probe/target binding region (column 15, lines 17-28).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the methods of Wittwer for monitoring and detecting nucleic acid hybridization of probes to target molecules using melting curve analysis and those of Picard for measuring binding affinities of probes containing unusual mutations such as two- and three-base mismatches or deletions, or multiple base mismatches separated by normal base pairs, since the methods of Wittwer are easily capable of measuring any known mutation including insertions and deletions where a probe can be designed to differ in melting temperature when hybridized to

mutant versus wild-type sequences (Wittwer, column 45, lines 60-67). Thus, an ordinary practitioner would have been motivated to use the melting profile methods of Wittwer to analyze the probe/target pairs taught by Picard containing modifications greater than single-base mismatches since probes with these types of changes can be prepared just as easily as those containing single nucleotide changes. Furthermore, since single mismatches impart at least a 4°C shift in the Tm of hybridization probes (Wittwer, column 42, lines 55-59), probes containing additional modifications will be even more readily distinguishable in melting profile analysis.

Conclusion

7. Claims 25-44 are rejected. No claims are allowable.

Correspondence

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David C. Thomas whose telephone number is 571-272-3320, and whose fax number is 571-273-3320. The examiner can normally be reached on 5 days, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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